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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Fycompa

perampanel

Procedure no: EMEA/H/C/002434/P46/020

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

Perampanel is a highly selective non-competitive AMPA-type glutamate receptor antagonist. In the EU, Fycompa (perampanel), following the recent extension of indication in the paediatric population (EMEA/H/C/002434/II/0047), is indicated for the adjunctive treatment of:

- partial-onset seizures (POS) with or without secondarily generalised seizures in patients from 4 years of age and older.

- primary generalised tonic-clonic (PGTC) seizures in patients from 7 years of age and older with idiopathic generalised epilepsy (IGE).

Perampanel has also been approved as monotherapy or adjunctive therapy in pediatric patients with POS aged 4 years and older in the US as of September 2018. The International Birth Date is 23 July 2012 in the EU (via the centralized procedure). Perampanel is marketed under the trade name Fycompa and is available as 2-, 4-, 6-, 8-, 10-, and 12-mg tablets and 0.5 mg/ml oral suspension.

With this post-authorisation measure (PAM) EISAI is hereby submitting final study results and report related to paediatric population in line with Article 46 of paediatric regulation 1901/2006, as amended, for **Study E2007-J000-335 (Study 335)**. Study 335 was a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel group study with an open-label extension phase in adults and adolescents aged 12 years and older who had a diagnosis of inadequately controlled partial-onset seizures. The study was conducted in Australia, China, Korea, Japan, Malaysia, Taiwan, and Thailand. Subjects were randomized to 1 of 4 treatment groups (4, 8, 12 mg/day of perampanel, or placebo) in a 1:1:1:1 ratio. The study randomised 710 subjects (planned 680 subjects, 170 subjects per treatment group) into the Core phase, 73 of whom were less than 18 years of age.

The primary objective of Study 335 was to confirm the efficacy of perampanel (4, 8, and 12 mg) compared to placebo given as an adjunctive therapy in subjects with refractory partial-onset seizures. The secondary objectives were a) to evaluate the safety and tolerability of perampanel compared to placebo given as an adjunctive therapy in subjects with refractory partial-onset seizures, b) to evaluate the long-term maintenance effect of perampanel (4, 8, and 12 mg) given as an adjunctive therapy in subjects with refractory partial-onset seizures, c) and to evaluate the pharmacokinetics (PK) of perampanel including the effects of concomitant antiepileptic drugs (AEDs) and to explore the relationship between PK and efficacy of perampanel.

This study E2007- J000-335 (Study 335) was completed on 02 Nov 2020. The submission of the final clinical study report for Study 335 is being made to the European Medicines Agency to fulfil the obligation to present data from any MAH-sponsored study in a paediatric population.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Post-authorisation measure - Submission of paediatric study pursuant to article 46 of Regulation (EC) No 1901/2006 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The investigational medicinal product tested in Study 335 was Fycompa as film-coated tablets of 2, 4, 6, 8, 10 and 12 mg.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for Study E2007-J000-335 (hereafter referred to as Study 335), a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study (Core Study) followed by the Extension Phase to confirm the efficacy and evaluate the safety and tolerability of perampanel compared to placebo given as an adjunctive therapy in subjects 12 years of age and older with refractory partial-onset seizures.

2.3.2. Clinical study

Description

The phase 3 study was divided into two parts: a double-blind, placebo-controlled, parallel-group Core study and an open label extension phase to evaluate the efficacy and safety of perampanel administered as an adjunctive therapy in subjects with refractory partial-onset seizures.

Methods

Objectives

Primary Objective:

The primary objective of the study is to confirm the efficacy of perampanel compared to placebo given as an adjunctive therapy in subjects with refractory partial-onset seizures

Secondary Objectives:

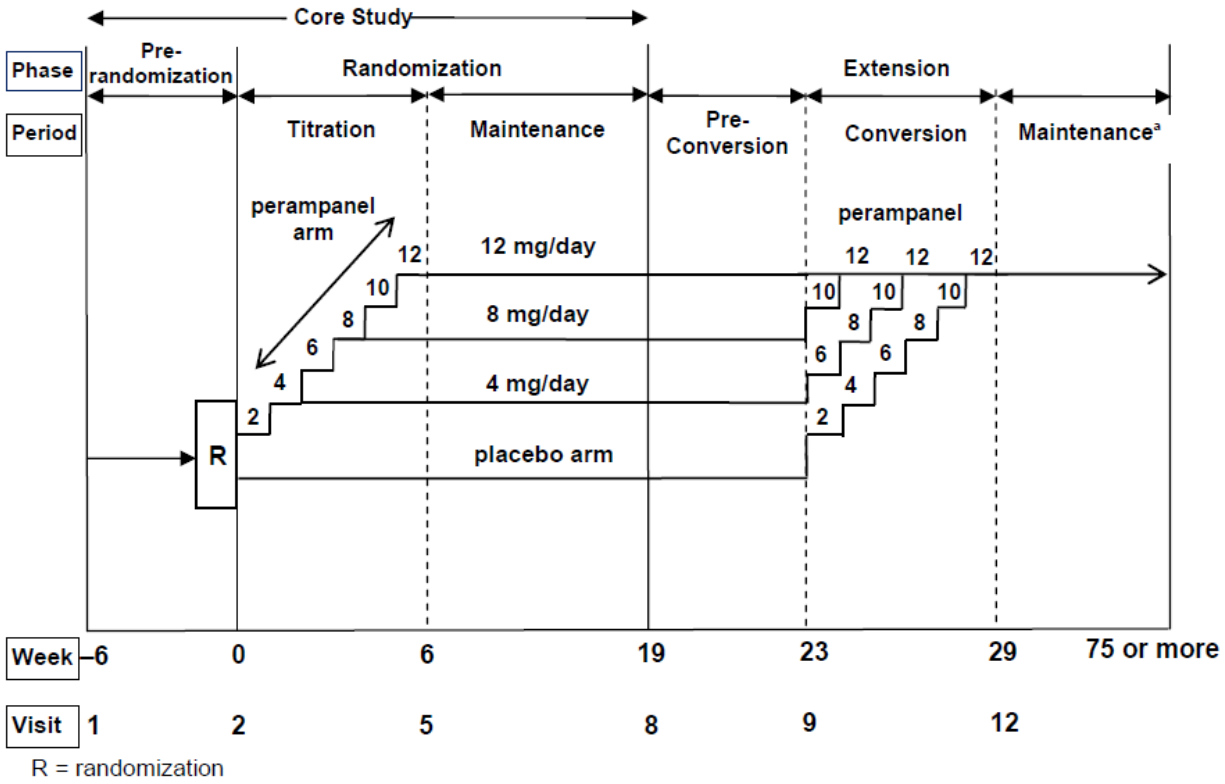
• To evaluate the *safety and tolerability* of perampanel compared to placebo given as an adjunctive therapy in subjects with refractory partial-onset seizures

• To evaluate the *long-term maintenance effect* of perampanel given as an adjunctive therapy in subjects with refractory partial-onset seizures

• To evaluate the *pharmacokinetics* (PK) of perampanel including the effects of concomitant antiepileptic drugs (AEDs) and to explore the *relationship between PK and efficacy of perampanel.*

Study design

Study 335 has been designed to confirm the efficacy of perampanel and to evaluate the safety and tolerability of perampanel prescribed as add-on therapy in patients with epilepsy in Australia, China, Korea, Japan and Malaysia. Subjects were randomized to 1 of 4 treatment groups (4, 8, 12 mg/day of perampanel, or placebo) in a 1:1:1:1 ratio. The figure below represents the overall study design:



a: Depending on the requirements in each country, the Maintenance Period of the Extension Phase was to be terminated within 3 months from the launch date of perampanel in the country or at Week 75, whichever is later.

CHMP comment:

*The **Core randomized study** consisted of 2 phases: prerandomization (6 weeks) and randomization (19 weeks). The randomization phase consisted of 2 periods: titration (6 weeks) and maintenance (13 weeks). During the prerandomization phase, subjects were assessed for their eligibility to participate, including seizure frequency. Once all eligibility criteria and none of the exclusion criteria met, subjects entered the randomization phase.*

The subjects were prestratified based on country and concomitant AEDs. Inducer AEDs are defined as carbamazepine, oxcarbazepine, phenytoin, vs non-inducer AED.

They were randomized to 1 of the 4 treatment groups (4, 8, 12 mg/day of perampanel, or placebo).

During the titration period, the dose was increased at weekly intervals in increments of 2 mg to a target dose of 4, 8, or 12 mg.

During the maintenance period, subjects entered this period on the last dose they achieved at the end of the titration period and continued taking this dose level once daily at bedtime until end of study. Adjustment of the study drug dose level during this period was not recommended. However, according to the investigator's clinical judgment, subjects experiencing intolerable AEs were allowed to have their dose reduced and increased again if tolerated.

For both periods, subjects who could not tolerate 2 mg dose were discontinued from the study.

*The **extension study** included subjects who completed the Core study. The extension phase consisted of 3 periods: preconversion (4 weeks, where subjects continued taking the same dose level as they took in the maintenance period of the Core Study in a blinded manner), conversion (6 weeks, where subjects previously assigned to the placebo group in the Core Study, began receiving perampanel 2 mg/day in a blinded manner and were up-titrated in weekly 2-mg increments to a maximum of 12 mg*

of perampanel or until an optimal dose was found), and maintenance (46 weeks or longer, where subjects were maintained with the perampanel dose that provided the optimal combination of efficacy and tolerability). A Follow-up visit was conducted 4 weeks after the last dose of perampanel was administered.

Overall, adjustment of the study drug dose level during this maintenance period was not recommended. However, according to the investigator's clinical judgment, subjects experiencing intolerable AEs were allowed to have their dose reduced if needed.

Study population /Sample size

The study planned to enrol 680 patients (170 subjects per treatment group).

Subjects were eligible for participation in the study if they were aged 12 years and older, with a clinical diagnosis of epilepsy with partial seizures with or without secondarily generalized seizures and who had been treated for at least 12 weeks but confirmed to be uncontrolled with more than 1 standard AED within the 2 years before Visit 1.

Randomized: 710 subjects (177in the placebo group, 176 in the perampanel 4 mg group, 177 in the perampanel 8 mg group, 180 in the perampanel 12 mg group).

Completed the Core Study: 599 subjects (152 in the placebo group, 156 in the perampanel 4 mg group, 147 in the perampanel 8 mg group, 144 in the perampanel 12 mg group).

Discontinued from the Core Study: 108 subjects.

Entered the Extension Phase: 596 subjects.

Sample size rationale: it was assumed that in comparison to the prerandomization phase, subjects would show a percent reduction in seizure frequency of 10% in the placebo treatment group and 30% in the 8 mg treatment group in the randomization phase of the ITT Analysis Set. Therefore, a sample size of 170 subjects for each treatment group in the ITT Analysis Set would have more than 80% power to detect a treatment difference in seizure frequency change of 20% (assuming a common standard deviation of 62%) between placebo and each of the active treatment groups based on Wilcoxon rank-sum test at a 0.05 2-sided significance level.

CHMP comment:

The patients were selected to receive Fycompa as an adjunctive treatment starting at Visit 1. The patients should also be treated with stable doses of 1, 2, or a maximum of 3 approved AEDs (only 1 inducer AED was allowed; i.e., carbamazepine, phenytoin, or oxcarbazepine).

The discontinuation rate from the Core study is rather acceptable (15%). The number of patients that entered the extension study (596) is nearly equivalent to the number of patients that completed the Core study (599) at week 19.

Treatments

Fycompa was taken as a single oral dose taken once daily before bedtime. Perampanel was supplied as 2-mg tablets. Treatment was initiated with a dose of 2 mg/day as approved in the PIL.

Comparator drug: Placebo was supplied as matching perampanel 2-mg tablets. Perampanel-matched placebo was also taken as a single oral dose taken once daily before bedtime.

The planned duration of treatment in this study was 75 weeks or longer. The duration of treatment in the Core study was 19 weeks and the planned total duration of treatment in the extension phase was a minimum of 56 weeks (for more details of each period, see table 1 above).

CHMP comment:

The dose was increased based on clinical response and tolerability by increments of 2 mg/day to a maintenance dose of 4 mg/day to 12 mg/day for at least 19 weeks or until 75 weeks if entering and completing the extension study.

Outcomes/endpoints

- Efficacy:

- *Percent change in seizure frequency per 28-days*: the seizure frequency and percent change from baseline in seizure frequency from the randomization phase until the maintenance period of the extension phase were summarized using descriptive statistics.

- *Response rate*: the number (percentage) of responder (ie, subjects who had at least a 50% reduction in seizure frequency per 28 days relative to baseline) from the randomization phase until the maintenance period of the extension phase was summarized.

- Safety:

- *All Adverse Events* (AEs) including Serious Adverse Events (SAEs).

- *Adverse Events of Special Interest* (AESI) such as Medication Errors, Lack of Therapeutic Efficacy, Overdose, Abuse, Misuse, Off Label Use, Pregnancy and exposure to drug during breast feeding.

- *TEAE*: the incidence of TEAEs, treatment-related TEAEs, serious TEAEs, TEAEs leading to discontinuation, TEAEs leading to dose reduction, and TEAEs leading to study drug interruption was summarized by SOC and PT, by maximum severity of TEAEs, by the time point of first onset of TEAEs and by the mean daily dose of perampanel.

CHMP comment:

The following assessments / procedures were carried out during the 75 weeks treatment period:

- Efficacy: The seizure counts and seizure types were recorded on the diary and by the investigator and this allows the assessment of the percent change in seizure frequency per 28 days and the responder rate.

- Safety: Examining and recording number and details of AEs, withdrawal from treatment, AESI and TEAE. Other safety findings like clinical laboratory tests (haematology, chemistry, and urinalysis), vital signs, weight, 12-lead electrocardiogram (ECG), Columbia-Suicide Severity Rating Scale (C-SSRS) were also recorded for assessment.

Efficacy is the primary endpoint and safety the secondary.

Two other outcomes were summarized in the CSR using descriptive statistics although not detailed in this report: Complex partial seizure and secondary generalized seizure frequency and the Clinical Global Impression of Change. A focus is made on the main efficacy criteria.

Furthermore, subgroup analyses for the seizure frequency and 50% responder rate were performed using the following subgroups: 1) country (Japan/China/Korea/Other), 2) baseline concomitant AEDs (inducer [carbamazepine/oxcarbazepine/phenytoin/overall], noninducer), 3) Japan and concomitant AEDs. This is not detailed in this report. These subgroup analyses are not displayed in this report.

Statistical Methods

The Intent-to-treat (ITT) Analysis Set included all subjects who signed informed consent, were randomized, received at least 1 dose of study medication, and had at least 1 post dose seizure frequency data.

All efficacy analyses were performed on the ITT Analysis Set. The results for the ITT Analysis Set were summarized by treatment group assigned in the randomization phase and by active treatment groups in the extension phase.

The Safety Analysis Set included all subjects who signed informed consent, were randomized, received at least 1 dose of perampanel, and had at least 1 post dose safety assessment.

CHMP comment:

The statistical methods are acceptable for the Core study and extension phase.

Results

Recruitment/ Number analysed

Table 1 extracted from the CSR displays the subject disposition and primary reason for discontinuation from the extension phase.

In total, 596 subjects entered the extension phase: 151 subjects in the placebo group, 156 subjects in the perampanel 4 mg group, 146 subjects in the perampanel 8 mg group, and 143 subjects in the perampanel 12 mg group.

table 1

Table 1 Subject Disposition and Primary Reason for Discontinuation From Extension Phase – All Randomized Subjects

	Placebo	Perampanel				Combined Total
		4 mg	8 mg	12 mg	Total	
Completed Core Study[a, b], n	152	156	147	144	447	599
Completed Core Study but not entered Extension Phase, n (%)	1 (0.7)	0	1 (0.7)	1 (0.7)	2 (0.4)	3 (0.5)
Entered Extension Phase, n (%)	151 (99.3)	156 (100.0)	146 (99.3)	143 (99.3)	445 (99.6)	596 (99.5)
Entered Extension Phase[c, d], n	151	156	146	143	445	596
Completed Extension Phase, n (%)	56 (37.1)	40 (25.6)	54 (37.0)	46 (32.2)	140 (31.5)	196 (32.9)
Discontinued Extension Phase, n (%)	95 (62.9)	116 (74.4)	92 (63.0)	97 (67.8)	305 (68.5)	400 (67.1)
Primary reason for discontinuation from Extension Phase[e], n (%)						
Adverse event	18 (11.9)	16 (10.3)	9 (6.2)	20 (14.0)	45 (10.1)	63 (10.6)
Lost to follow-up	2 (1.3)	1 (0.6)	1 (0.7)	1 (0.7)	3 (0.7)	5 (0.8)
Subject choice	37 (24.5)	40 (25.6)	39 (26.7)	28 (19.6)	107 (24.0)	144 (24.2)
Inadequate therapeutic effect	17 (11.3)	33 (21.2)	26 (17.8)	24 (16.8)	83 (18.7)	100 (16.8)
Withdrawal of consent	6 (4.0)	8 (5.1)	3 (2.1)	5 (3.5)	16 (3.6)	22 (3.7)
Pregnancy	2 (1.3)	0	1 (0.7)	1 (0.7)	2 (0.4)	4 (0.7)
Other[f]	13 (8.6)	18 (11.5)	13 (8.9)	18 (12.6)	49 (11.0)	62 (10.4)

CHMP comment:

The study was conducted at 119 sites in Australia (7 sites), China (22 sites), Korea (14 sites), Japan (61 sites), Malaysia (5 sites), Taiwan (5 sites), and Thailand (5 sites).

Of the 596 subjects, 196 completed the extension Phase and 400 were discontinued from the extension phase. Overall, the most common primary reasons for discontinuation from the extension phase were subject choice (24.2%), inadequate therapeutic effect (16.8%), AE (10.6%), and other (10.4%). 400 subjects that discontinued the study represents two thirds (67%) of all participants at week 75. Regarding the high rate of discontinuation, any conclusion based on these end-of-study data could not be considered as reliable.

Baseline data

Table 1 extracted from the CO summarizes the demography, baseline characteristics, and epilepsy-specific medical history for the Safety Analysis Set.

table 2

Table 1 Demography, Baseline Height, Weight, and BMI – Entire Study: ITT Analysis Set

Category	Placebo (N=175)	Perampanel				Combined Total (N=704)
		4 mg (N=174)	8 mg (N=175)	12 mg (N=180)	Total (N=529)	
Age (year)[a]						
n	175	174	175	180	529	704
Mean (SD)	34.5 (13.22)	33.1 (13.23)	33.6 (14.11)	32.3 (12.30)	33.0 (13.21)	33.4 (13.22)
Median	32.0	32.0	32.0	30.5	31.0	32.0
Min, Max	12, 71	12, 68	12, 68	12, 69	12, 69	12, 71
Age group, n (%)						
<18	12 (6.9)	23 (13.2)	25 (14.3)	14 (7.8)	62 (11.7)	74 (10.5)
18 to <65	160 (91.4)	150 (86.2)	146 (83.4)	164 (91.1)	460 (87.0)	620 (88.1)
≥65	3 (1.7)	1 (0.6)	4 (2.3)	2 (1.1)	7 (1.3)	10 (1.4)
Sex, n (%)						
Male	86 (49.1)	80 (46.0)	91 (52.0)	87 (48.3)	258 (48.8)	344 (48.9)
Female	89 (50.9)	94 (54.0)	84 (48.0)	93 (51.7)	271 (51.2)	360 (51.1)
Country, n (%)						
Japan	60 (34.3)	61 (35.1)	61 (34.9)	63 (35.0)	185 (35.0)	245 (34.8)
Korea	44 (25.1)	44 (25.3)	41 (23.4)	42 (23.3)	127 (24.0)	171 (24.3)
China	45 (25.7)	43 (24.7)	48 (27.4)	46 (25.6)	137 (25.9)	182 (25.9)
Other[b]	26 (14.9)	26 (14.9)	25 (14.3)	29 (16.1)	80 (15.1)	106 (15.1)
Race, n (%)						
White	7 (4.0)	7 (4.0)	14 (8.0)	7 (3.9)	28 (5.3)	35 (5.0)
Black or African American	0	0	0	0	0	0
Japanese	60 (34.3)	61 (35.1)	61 (34.9)	63 (35.0)	185 (35.0)	245 (34.8)
Chinese	48 (27.4)	49 (28.2)	50 (28.6)	52 (28.9)	151 (28.5)	199 (28.3)
Korean	44 (25.1)	44 (25.3)	41 (23.4)	41 (22.8)	126 (23.8)	170 (24.1)
Other Asian	16 (9.1)	12 (6.9)	7 (4.0)	15 (8.3)	34 (6.4)	50 (7.1)
American Indian or Alaska Native	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	1 (0.6)	0	1 (0.2)	1 (0.1)
Other	0	1 (0.6)	1 (0.6)	2 (1.1)	4 (0.8)	4 (0.6)

table 3

Table 1 Demography, Baseline Height, Weight, and BMI – Entire Study: ITT Analysis Set

Category	Placebo (N=175)	Perampanel				Combined Total (N=704)
		4 mg (N=174)	8 mg (N=175)	12 mg (N=180)	Total (N=529)	
Weight (kg)[a]						
n	172	172	175	178	525	697
Mean (SD)	61.78 (14.452)	61.69 (14.421)	62.09 (16.231)	60.87 (15.460)	61.55 (15.373)	61.60 (15.141)
Median	60.25	61.80	59.00	59.80	60.00	60.00
Min, Max	24.5, 111.0	19.0, 114.0	32.0, 123.6	26.0, 113.8	19.0, 123.6	19.0, 123.6
Height (cm)[a]						
n	172	174	174	176	524	696
Mean (SD)	162.63 (9.439)	162.78 (9.360)	162.91 (9.617)	163.37 (9.863)	163.02 (9.601)	162.93 (9.556)
Median	163.05	162.00	162.25	163.00	162.60	162.70
Min, Max	135.3, 190.0	125.0, 183.6	137.9, 191.0	135.0, 188.7	125.0, 191.0	125.0, 191.0
BMI (kg/m^2)[a]						
n	172	174	174	176	524	696
Mean (SD)	22.99 (4.283)	23.03 (4.381)	23.10 (5.020)	22.53 (4.412)	22.89 (4.611)	22.91 (4.530)
Median	22.35	22.75	22.10	22.15	22.25	22.30
Min, Max	12.3, 38.1	11.9, 37.6	14.1, 45.9	11.1, 44.9	11.1, 45.9	11.1, 45.9

Percentages are based on the total number of subjects with nonmissing values in the relevant treatment group.
BMI = body mass index, ITT = intent-to-treat, Max = maximum, Min = minimum.
a: Age is calculated at date of informed consent. Weight, at baseline. Height and BMI, at Visit 1.
b: Other consists of 4 countries: Australia, Malaysia, Taiwan, and Thailand.
Source: Core study CSR Table 8

CHMP comment:

Baseline demographic characteristics and epilepsy-specific medical history were balanced across the treatment groups. Most (88.1%) of the 704 subjects in the ITT Analysis Set were 18 to 64 years old. There were 74 (10.5%) subjects less than 18 years old, and 10 (1.4%) subjects were 65 years of age.

The mean ± SD age was 33.4±13.22 years. Overall, 48.9% of the subjects were male. The highest percentage of subjects by country was 35.5% in Japan. Korea and China were nearly similar with 23.7% and 25.6%. The median time since diagnosis was 182.00 months (range: 8.0, 666.0) i.e. around 15 years.

Complex partial seizures were the most common seizure type (85.4%) whereas simple partial seizures without motor signs were the less common seizure type (25.5%).

Regarding the concomitant medications, all subjects were taking AEDs at baseline. Of all the subjects, over 50% were taking 3 AEDs and approximately 67% were taking at least 1 inducing AED at baseline. (43.7% for carbamazepine, 13.8% for oxcarbazepine, and 9.7% for phenytoin). The most common non-inducing AEDs used at baseline were valproic acid (41.4%), levetiracetam (40.8%), and lamotrigine (27.2%).

The paediatrics (< 18 years of age) are underrepresented, which undermines the validity of the study in this age cohort. No firm conclusion concerning this age group is therefore possible.

Pharmacokinetic results

The Pharmacokinetic Analysis Set included subjects who had at least 1 evaluable plasma concentration. Of all randomized subjects (710 subjects), 1 subject was excluded from the Pharmacokinetic Analysis Set because the subject received an incorrect study drug kit.

A total of 709 subjects (placebo group, n = 176; perampanel 4 mg group, n = 176; perampanel 8 mg group, n = 177; and perampanel 12 mg group, n = 180) were included.

Core Study

Summaries of plasma perampanel concentrations by treatment group except for placebo group are summarized for population PK and PK/PD analysis. The details were described in the separately prepared analysis plan and its report.

Extension Phase

PK assessments were not performed during the Extension Phase.

CHMP comment:

To evaluate the pharmacokinetics (PK) of perampanel including the effects of concomitant antiepileptic drugs (AEDs) and to explore the relationship between PK and efficacy of perampanel was defined as a secondary endpoint of this study. However, the PK results are not submitted in an assessable format. As these data were previously submitted and discussed for assessment of PK data in adults and adolescents, this concern is not pursued.

Efficacy results

The Intent-to-Treat (ITT) Analysis Set (704 subjects) was the primary analysis set used for efficacy analyses. Of all randomized subjects (710 subjects), 6 subjects were excluded from the ITT Analysis Set because they did not receive any study drug or did not have any post-dose seizure data. There was a total of 74 subjects aged 12 to < 18 years (Placebo group, n = 12; perampanel 4 mg group, n = 23; perampanel 8 mg group, n = 25; and perampanel 12 mg group, n = 14) in ITT Analysis Set.

During the study, two main efficacy parameters were evaluated: percent change in seizure frequency per 28 days and responder rate.

1. Percent Change in Seizure Frequency per 28 Days

The seizure frequency and percent change from baseline in seizure frequency per 28 days during each phase/period (stratified by the treatment assigned in the Core study) for the Core study and the extension phase were summarized in table 4:

table 4

Table 4 Percent Change From Prerandomization Phase (Baseline) in Seizure Frequency per 28 Days – Extension Phase (Final): ITT Analysis Set

Parameter Statistic	Prior Placebo (N=175)	Prior Perampanel (N=529)
Prerandomization Phase Seizure Frequency		
n	175	529
Mean (SD)	29.47 (67.588)	21.36 (37.367)
Median	10.00	9.55
Min, Max	3.1, 618.0	2.7, 388.5
Percent Change to Randomization Phase		
n	175	529
Mean (SD)	–1.02 (62.629)	–13.95 (78.446)
Median	–10.76	–26.57
Min, Max	–90.4, 400.0	–100.0, 809.4
Percent Change to Preconversion Period		
n	150	440
Mean (SD)	–12.84 (65.860)	–3.91 (340.970)
Median	–16.50	–36.72
Min, Max	–100.0, 375.0	–100.0, 5851.9
Percent Change to Conversion Period		
n	148	434
Mean (SD)	–36.06 (59.784)	–23.02 (133.636)
Median	–48.87	–43.26
Min, Max	–100.0, 294.7	–100.0, 2055.8
Percent Change to Maintenance Period of Extension Phase (Weeks 30 – 47)		
n	135	407
Mean (SD)	–33.10 (69.718)	–31.24 (94.400)
Median	–44.43	–46.15
Min, Max	–100.0, 405.8	–100.0, 1367.1
Percent Change to Maintenance Period of Extension Phase (Weeks 48 – 55)		
n	117	338
Mean (SD)	–22.96 (125.146)	–40.58 (72.886)
Median	–43.69	–53.85
Min, Max	–100.0, 984.5	–100.0, 700.8
Percent Change to Maintenance Period of Extension Phase (Weeks 56 – 63)		
n	109	323
Mean (SD)	–23.87 (163.518)	–38.20 (81.822)
Median	–49.00	–52.00
Min, Max	–100.0, 1576.4	–100.0, 798.6
Percent Change to Maintenance Period of Extension Phase (Weeks 64 – 75)		
n	103	304
Mean (SD)	–31.79 (125.136)	–41.64 (69.936)
Median	–47.62	–55.93
Min, Max	–100.0, 1102.8	–100.0, 521.1

The median percent changes from baseline in seizure frequency per 28 days during the Core study and each period of the extension study (Preconversion Period, Conversion Period, Weeks 30 to 47, Weeks 48 to 55, Weeks 56 to 63 and Weeks 64 to 75) in subjects who previously received placebo were respectively –10.76%, –16.50%, –48.87%, –44.43%, –43.69%, –49.00%, and –47.62%.

For those patients who previously received perampanel, the median percent changes were respectively –26.57%, –36.72%, –43.26%, –46.15%, –53.85%, –52.00%, and –55.93%, respectively.

When comparing the results according to the perampanel dosing, during the Core study, the treatment differences from placebo were statistically significant for the perampanel 8 mg group (p=0.0003) and 12 mg group (p<0.0001), but not for the perampanel 4 mg group (p=0.2330).

According to the CO, it seems that when focusing on the subanalyses for patients aged 12 to < 18 years, the median percent change in seizure frequency per 28 days during the Core study was -9.25% in the placebo group, -5.82% in the perampanel 4 mg group, -15.11% in the perampanel 8 mg group, and -63.71% in the perampanel 12 mg group. The median treatment differences from placebo were estimated to be 4.09%, -12.68%, and -51.62% respectively for the perampanel 4, 8, and 12 mg groups.

CHMP comment:

During the Core study, the treatment differences from placebo were statistically significant for the perampanel 8 mg group (p=0.0003) and 12 mg group (p<0.0001), but not for the perampanel 4 mg group.

During the extension phase, the median percent reduction in seizure frequency in the subjects who previously received placebo changes similarly to that in the subjects who previously received perampanel. The median percent change in seizure frequency shows that the efficacy of perampanel established in the Core study is maintained throughout the extension phase. This result is however to be considered cautiously taking into account the high level of discontinuation during the extension phase (67%).

For the paediatric subgroup, the subanalysis concluded that the median treatment differences in seizure frequency from placebo are weak for the perampanel 4 and 8 mg groups (4.09% and -12.68% respectively) and rather high for the perampanel 12 mg group (-51.62%). The MAH is requested to provide a detailed table with the median percent change in seizure frequency per 28 days in paediatrics during the Core study and the extension study for each dosage compared to placebo. These results should be discussed by the MAH.

Overall, these data do not challenge the known efficacy results for perampanel in the studied population, in adults and adolescents.

2. Responder Rate

The responder rate (ie, subjects who had at least a 50% reduction in seizure frequency per 28 days relative to baseline) during each phase/period (stratified by the treatment assigned in the Core study) for the Core study and the extension phase were summarized in table 5:

table 5

Table 5 Responder Analysis – Extension Phase (Final): ITT Analysis Set

Analysis Window Responder	Prior Placebo (N=175) n (%)	Prior Perampanel (N=529) n (%)
Randomization Phase		
Yes	24 (13.7)	165 (31.2)
No	151 (86.3)	364 (68.8)
Total	175 (100.0)	529 (100.0)
Preconversion Period		
Yes	42 (28.0)	179 (40.7)
No	108 (72.0)	261 (59.3)
Total	150 (100.0)	440 (100.0)
Conversion Period		
Yes	73 (49.3)	192 (44.2)
No	75 (50.7)	242 (55.8)
Total	148 (100.0)	434 (100.0)
Maintenance Period of Extension Phase (Weeks 30 – 47)		
Yes	60 (44.4)	192 (47.2)
No	75 (55.6)	215 (52.8)
Total	135 (100.0)	407 (100.0)
Maintenance Period of Extension Phase (Weeks 48 – 55)		
Yes	54 (46.2)	182 (53.8)
No	63 (53.8)	156 (46.2)
Total	117 (100.0)	338 (100.0)
Maintenance Period of Extension Phase (Weeks 56 – 63)		
Yes	54 (49.5)	176 (54.5)
No	55 (50.5)	147 (45.5)
Total	109 (100.0)	323 (100.0)
Maintenance Period of Extension Phase (Weeks 64 – 75)		
Yes	50 (48.5)	165 (54.3)
No	53 (51.5)	139 (45.7)
Total	103 (100.0)	304 (100.0)

A responder is a subject who experienced a 50% or greater reduction in seizure frequency per 28 days from the Prerandomization Phase.
Percentages are based on the total number of subjects in relevant treatment group.
ITT = intent-to-treat.
Source: Table 14.2.1.2.2.1.1

Overall, the 50% responder rates for all partial seizures during the Core study were greater in the perampanel 4 mg group (23.0%), the perampanel 8 mg group (36.0%) and the perampanel 12 mg group (43.3%) than in the placebo group (19.4%). The p values for the differences from placebo were 0.3954 for the perampanel 4 mg group, 0.0005 for the perampanel 8 mg group, and <0.0001 for the perampanel 12 mg group.

During the extension phase, the 50% responder rates in the subjects who previously received placebo changes similarly to that in the subjects who previously received perampanel. This indicated that efficacy established in the Core study was maintained throughout the extension phase.

According to the CO, it seems that when focusing on the subanalyses for patients aged 12 to < 18 years, the 50% responder rate for all partial seizures during the Core study was 25.0% in the placebo-group, 13.0% in the perampanel 4 mg group, 20.0% in the perampanel 8 mg group and 78.6% in the perampanel 12 mg group respectively.

CHMP comment:

During the Core study, the responder rate is significantly greater in the perampanel 8 mg group (p = 0.0005) and 12 mg group (p < 0.0001) compared to placebo group. This result is not significant for the 4 mg group. The responder rate is maintained throughout the extension phase. These data do not challenge the known efficacy results for perampanel in the studied population, in adults and adolescents. This result is however to be considered cautiously taking into account the high level of discontinuation during the extension phase (67%).

For the paediatric subgroup, the subanalysis concluded that the responder rate is weaker for the perampanel 4 and 8 mg groups (13% and 20% respectively) than for placebo (25%) and rather high for the perampanel 12 mg group 78.6%). The MAH is requested to provide a detailed table with the responder rate in paediatrics during the Core study and the extension study for each dosage compared to placebo. These results should be discussed by the MAH.

Overall, these data do not challenge the known efficacy results for perampanel in the studied population, in adults and adolescents.

Safety results

For the safety variables, the data collected during the perampanel treatment in the entire study (Core Study plus Extension Phase) were summarized for the Safety Analysis Set.

Extent of Exposure

For the Core study, the Safety Analysis Set (707 subjects) included the group of randomized subjects who received study drug and had at least 1 post baseline safety assessment. Of all randomized subjects (710 subjects), 3 subjects were excluded from the Safety Analysis Set because they did not receive any study drug. Of the 707 subjects, 74 were the subjects aged 12 to <18 years.

For the extension phase, the Safety Analysis Set (679 subjects) included the group of randomized subjects who received at least 1 dose of perampanel and had at least 1 post dose safety assessment. Of 710 randomized subjects, 31 were excluded from the Safety Analysis Set because they did not receive any dose of perampanel. Of the 679 subjects, 73 were the subjects aged 12 to <18 years.

Overall, 67.0% of the subjects received perampanel for more than 12 months (336 days). And 41.7% of the subjects received perampanel for more than 24 months (672 days).

Overall, 51.8% of the subjects received a perampanel daily dose of 12 mg at last dose. And the mean perampanel dose received is 9.81 mg (SD±2.852).

CHMP comment:

The Safety Analysis Set is rather substantial for gathering safety long-term data.

The actual administered daily doses are in accordance with the dosing recommendations already approved in the SmPC for children above 12 years of age and adults for the treatment of POS, in conjunction with other AED.

Adverse events

Adverse events refers to TEAEs (ie, an adverse event that emerges after study treatment initiation until the last visit of the study or within 30 days after the last study treatment). TEAEs were summarized by SOC and PT for the Safety Analysis Set.

An overview of TEAE is displayed in table 6:

table 6

Table 13 Overview of Treatment-Emergent Adverse Events – Extension Phase (Final): Safety Analysis Set

Category	Total Perampanel (N=679) n (%)
TEAEs	624 (91.9)
Treatment-related TEAEs[a]	531 (78.2)
Severe TEAEs	75 (11.0)
Serious TEAEs	113 (16.6)
Deaths[b]	7 (1.0)
Other SAEs[c]	110 (16.2)
Life threatening	4 (0.6)
Requires inpatient hospitalization or prolongation of existing hospitalization	104 (15.3)
Persistent or significant disability or incapacity	0
Congenital anomaly/birth defect	0
Important medical events	10 (1.5)
TEAEs Leading to Study Drug Dose Adjustment	365 (53.8)
TEAEs Leading to Study/Study Drug Withdrawal	141 (20.8)
TEAEs Leading to Study Drug Dose Reduction	265 (39.0)
TEAEs Leading to Study Drug Dose Interruption	4 (0.6)

Percentages are based on the total number of subjects in perampanel treatment groups.
For each row category, a subject with 2 or more TEAEs in that category is counted only once.
TEAE is defined as an adverse event that emerges from the first dose of the study drug to the last visit of the study or on or after 30 days since the last dose of study drug, whichever comes later, having been absent at pretreatment (Baseline), re-emerges during treatment, having been present at Baseline but stopped prior to treatment, or worsens in severity during treatment relative to the pretreatment state, when the adverse event is continuous.
SAE = serious adverse event, TEAE = treatment-emergent adverse event.
a: Includes TEAEs considered by the investigator to be possibly or probably related to study drug or TEAEs with missing causality.
b: Includes all subjects with an SAE resulting in death.
c: If a subject had both fatal and nonfatal SAEs, the subject is counted in the previous row and is also counted in this row.
Source: Table 14.3.1.2.2.1

CHMP comment:

TEAE occurred in 624 (91.9%) subjects, treatment-related TEAE in 531 (78.2%) subjects and severe TEAE in 75 (11.0%) subjects.

There were 113 (16.6%) serious TEAE, among them 7 deaths (1.0%) and 104 subjects requiring inpatient hospitalization or prolongation of existing hospitalization (15.3%).

For the TEAE leading to study drug dose adjustment, most cases led to a dose reduction for 39% of subjects or to study/drug withdrawal in 20.8% of subjects.

Summary of TEAE

Core Study

- **Common TEAE**

TEAEs occurred in 117 subjects (66.5%) in the placebo group, 121 subjects (68.8%) in the perampanel 4 mg group, 129 subjects (73.7%) in the perampanel 8 mg group, and 156 subjects (86.7%) in the perampanel 12 mg group. The most frequently (≥10%) reported TEAEs were:

- **nasopharyngitis** (14.8%) and **somnolence** (13.1%) in the placebo group;

- **dizziness**, **somnolence**, and **nasopharyngitis** across all perampanel treatment groups (perampanel 4 mg group, 22.7%, 15.9% and 13.1%; perampanel 8 mg group, 28.6%, 17.7% and 13.7%; and perampanel 12 mg group, 42.2%, 17.8% and 12.8%, respectively).

The following TEAEs occurred at a frequency of 5% or more and at rates that were at least twice as high in any of the perampanel groups as those in the placebo group: **dizziness**, **irritability**, **gait disturbance**, and **rash**.

When focusing on TEAE reported during the Core Study for adolescent subjects (aged 12 to <18 years), the most frequently (≥10%) reported TEAEs in adolescent subjects were:

- **dizziness** (30.4%), **somnolence**, **nasopharyngitis** and **upper respiratory tract infection** (13.0% each) in the perampanel 4 mg group,

- **nasopharyngitis** (24.0%), **somnolence** (16.0%), and **dizziness** (12.0%), in the perampanel 8 mg group,

- **dizziness** and **somnolence** (35.7% each), **upper respiratory tract infection** (21.4%), and **weight increased**, **blood creatine phosphokinase increased** and **headache** (14.3% each) in the perampanel 12 mg group.

CHMP comment:

Dizziness increases in a dose-dependent fashion as its occurrence increases with the perampanel dosing groups (22.7% for perampanel 4 mg group, 28.6% for perampanel 8 mg group and 42.2% for perampanel 12 mg group). This is confirmed by the PI: "The adverse reactions most commonly (≥ 1% in the total perampanel group and greater than placebo) leading to discontinuation were dizziness and somnolence" and in section 4.8 Undesirable effects dizziness is classified as a very common AE (≥ 1/10).

The most frequently (≥10%) reported treatment-related TEAEs were dizziness and somnolence across all perampanel treatment groups (perampanel 4 mg group, 22.2% and 15.3%; perampanel 8 mg group, 28.0% and 17.1%; and perampanel 12 mg group, 40.6% and 16.7%, respectively) as compared to the placebo group. No treatment-related TEAE was reported by ≥10% of the subjects in the placebo group.

- **Deaths**

There were a total of 2 deaths during treatment or within 30 days after the last dose in the Core Study, 1 subject each in the placebo and the perampanel 8 mg group. No death was assessed as related to study treatment. There was no death in the 12 to <18 years age group.

- **Treatment-emergent SAEs**

Treatment-emergent SAEs (including fatalities) occurred in 10 subjects (5.7%) in the placebo group, 6 subjects (3.4%) in the perampanel 4 mg group, 7 subjects (4.0%) in the perampanel 8 mg group, and 12 subjects (6.7%) in the perampanel 12 mg group.

In the 12 to <18 years age group, treatment-emergent SAEs occurred in 2 subjects (14.3%) in the perampanel 12 mg group.

With the exception of the 2 subjects who died as a result of a SAE, most subjects recovered from their SAE with no sequelae during the Core Study. Most SAEs were considered not related to study drug.

CHMP comment:

The treatment emergent SAE and the deaths that occurred in the overall study are detailed in the extension period.

- **TEAEs leading to discontinuation of study / study drug**

TEAEs leading to discontinuation of study or study drug occurred in 6 subjects (3.4%) in the placebo group, 8 subjects (4.5%) in the perampanel 4 mg group, 20 subjects (11.4%) in the perampanel 8 mg group, and 25 subjects (13.9%) in the perampanel 12 mg group.

In the 12 to <18 years age group, TEAEs leading to discontinuation of study or study drug occurred in 1 subject (8.3%) in the placebo group, 1 subject (4.3%) in the perampanel 4 mg group, 1 subject (4.0%) in the perampanel 8 mg group, and 2 subjects (14.3%) in the perampanel 12 mg group, respectively.

Overall, the percentage of subjects with such TEAEs was higher in the perampanel 8 mg and 12 mg groups than in the placebo group. **Dizziness** was the event that most commonly led to study or study drug discontinuation in the perampanel groups compared with the placebo group.

CHMP comment:

The results of this core study are in compliance with the information displayed in the PI, i.e.: "the adverse reactions most commonly (≥ 1% in the total perampanel group and greater than placebo) leading to discontinuation were dizziness and somnolence". Thus the safety data of this core study confirms the known safety profile of perampanel in adults and adolescents.

Extension Phase

Summaries for the Extension Phase include only TEAEs that occurred on or after the first day of perampanel treatment in the entire study (Core Study and Extension Phase).

- **Common TEAE**

The TEAEs that occurred in at least 10% of the subjects were **dizziness** (46.8%), **nasopharyngitis** (25.2%), **somnolence** (24.3%), **headache** (13.8%), and **upper respiratory tract infection** (10.3%).

The treatment-related TEAEs that occurred in at least 10% of the subjects were dizziness (44.6%) and somnolence (23.0%).

When focusing on TEAE reported during the Core Study for adolescent subjects (aged 12 to <18 years), the most frequently (≥ 10%) reported TEAEs in adolescent subjects were **nasopharyngitis** (35.6%), **dizziness** (32.9%), **somnolence** (31.5%), **upper respiratory tract infection** (20.5%), **influenza** (13.7%), **headache** (11.0%), and **pyrexia** (11.0%).

CHMP comment:

The safety profile shown during the extension phase is similar to that of the core study.

- **Deaths**

Seven deaths during perampanel treatment or within 30 days after the last dose of perampanel were reported in the entire study (including the 2 events that occurred during the Core Study).

table 7

Table 15 Listing of Treatment-Emergent Deaths – Extension Phase (Final): All Subjects Treated With Perampanel

Subject ID Age (year), Sex, Race	Total Number of Days on Therapy[a]	Study Day of Death[b]/ Study Day of Death[c]	Day of Death in Relation to Last Dose[d]	Study Phase of AE Onset/ Last Dose Prior to Death	Cause of Death (MedDRA Preferred Term)	Study Day of AE Onset[e]/ Study Day of AE Onset[f]	Relationship to Study Drug
Prior Placebo							
[redacted] 59, [redacted]	654	819/655	2	Extension/ 12 mg	Asphyxia	819/655	Not related
[redacted] 44, [redacted]	382	544/383	2	Extension/ 12 mg	Sepsis	542/381	Not related
[redacted] 29, [redacted]	225	395/233	9	Extension/ 12 mg	Head injury	388/226	Not related
[redacted] 26, [redacted]	432	595/433	2	Extension/ 8 mg	[redacted]	595/433	Not related
Prior Perampanel 4 mg							
[redacted] [redacted] 12 to <18	174	181/181	8	Extension/ 6 mg	Immune thrombocytopenic purpura	158/158	Not related
				Follow-up/ 6 mg	Haemorrhage intracranial/Brain stem death secondary to intracranial bleed[g]	181/181	Not related
				Follow-up/ 6 mg	Haemorrhage intracranial/Intracranial Bleed[g]	181/181	Not related
Prior Perampanel 8 mg							
[redacted] 51, [redacted]	14	19/19	6	Follow-up/ 4 mg	Death	19/19	Not related
Prior Perampanel 12 mg							
[redacted] 25, [redacted]	254	255/255	2	Extension/ 12 mg	Sudden unexplained death in epilepsy	255/255	Possibly related

CHMP comment:

Of the 7 deaths, 6 were considered unrelated to the study drug. The other death, caused by a sudden unexplained death in epilepsy (SUDEP), was considered possibly related to the study drug by the investigator.

There was one death in the 12 to <18 years age group. A [redacted] *subject died due to immune thrombocytopenic purpura, haemorrhage intracranial and haemorrhage intracranial. All 3 events that occurred in this subject were considered unrelated to the study drug by the investigator.*

- **Treatment-emergent SAEs**

Treatment-emergent SAEs were reported in 113 subjects (16.6%) in the Safety Analysis Set.

Treatment-emergent SAEs that occurred in more than 1 subject were:

- status epilepticus (6 subjects; 0.9%),

- pneumonia, epilepsy and seizure (5 subjects; 0.7% each),

- cataract, contusion, skin laceration and abortion induced (4 subjects; 0.6% each),

- ankle fracture, brain contusion, intervertebral disc protrusion, aggression and suicide attempt (3 subjects; 0.4% each),

- and pyelonephritis acute, road traffic accident, hypernatremia, osteoarthritis, altered state of consciousness, dizziness, haemorrhage intracranial, partial seizures with secondary generalization, seizure cluster, pregnancy, postictal psychosis and psychotic disorder (2 subjects; 0.3%).

CHMP comment:

Most of the treatment-emergent SAEs were considered unrelated to the study drug and resolved with appropriate measures such as medication.

Most of the subjects recovered without sequelae from the treatment-emergent SAEs. Except one fatal treatment-emergent SAE (case of SUDEP considered possibly related to the study drug seen previously among the deaths), 32 treatment-emergent SAEs were considered related (possibly related and probably related) to the study drug by the investigator in 27/113 subjects.

- **TEAEs leading to discontinuation of study or study drug**

TEAEs leading to discontinuation (study or drug withdrawal) were reported in 141 subjects (20.8%).

In the 12 to <18 years age group, those TEAEs were reported in 15 subjects (20.5%).

TEAEs leading to discontinuation that occurred in more than 3 subjects (0.4%) were **dizziness** (25 subjects; 3.7%), **irritability** (16 subjects; 2.4%), **aggression** (11 subjects; 1.6%), **somnolence** (10 subjects; 1.5%), **nausea, ataxia and balance disorder** (5 subjects; 0.7% each), and **fatigue**, **seizure**, **pregnancy**, **suicidal ideation**, **suicidal attempt** and **rash** (4 subjects; 0.6% each).

CHMP comment:

The safety profile shown during the extension phase is overall similar to that of the core study or to the known safety profile as described in the PI. Indeed, all the AE described above leading to discontinuation of study or study drug (in particular dizziness and irritability) are already stated in section 4.8 of the SmPC of perampanel.

In the SmPC, it is stated: "The adverse reactions most commonly (≥ 1% in the total perampanel group and greater than placebo) leading to discontinuation were dizziness and somnolence" . Therefore, this is overall in line with what was observed in controlled phase 3 studies assessing the efficacy and safety of perampanel when given for the treatment of POS in adjunction to other AED.

Other Safety Findings

There were no changes of clinical importance in mean and median laboratory values over time. The incidence of markedly abnormal laboratory values was low and generally comparable across the 4 treatment groups.

There were no changes of clinical importance in mean and median vital signs and weight over time. The incidence of clinically notable values for systolic blood pressure, diastolic blood pressure, and pulse rate was low and comparable across the 4 treatment groups.

Clinically notable elevations in body weight occurred in a higher percentage of subjects in the perampanel groups than in the placebo group.

There were no changes of clinical importance in mean and median ECG parameters over time. Regarding QTc assessments, no clinically significant results were found.

There were no reports of abuse, misuse, or overdose with perampanel.

The incidence of TEAEs related to suicidal ideation or behaviour, while low, was higher in the perampanel groups than in the placebo group. The incidence of treatment-emergent suicidal ideation or behaviour based on the C-SSRS results was 7.7% in the Safety Analysis Set, although comparable across the 4 treatment groups.

CHMP comment:

Regarding laboratory values, vital signs, blood pressure measurements and ECG parameters, there were no notable changes of clinical importance in this study and the rate of changes were comparable across the treatments groups and the placebo group.

There were clinically notable elevations in body weight that occurred in a higher percentage of subjects in the perampanel groups than in the placebo group. The weight increase is an AE already stated in section 4.8 of the SmPC as a common AE.

The incidence of TEAEs related to suicidal ideation or behaviour, while low, was higher in the perampanel groups than in the placebo group, although comparable across the 4 treatment groups. The suicidal ideation and suicidal attempt are AEs already stated in section 4.8 of the SmPC as uncommon AEs. The incidence of the AEs seems higher that uncommon in this study, however it is difficult to draw any conclusion on its frequency as the recording of these AEs is probably not similar between the blinded phase 3 studies and this extension study.

2.3.3. Discussion on clinical aspects

The aim of this study was to evaluate the efficacy and safety of Fycompa (perampanel) as an adjunctive treatment of partial-onset seizures in adults and adolescents.

Fycompa was taken as a single oral dose once daily. The drug was taken at doses of 4 mg/day to 12 mg/day to be effective therapy in partial-onset seizures. The drug was initiated with a dose of 2 mg/day as per the approved package insert. The dose was increased based on clinical response and tolerability by increments of 2 mg/day to a maintenance dose of 4 mg/day to 12 mg/day.

The primary endpoint for the core study was efficacy and for the extension period it was the safety on a long-term manner.

Regarding the efficacy, perampanel has shown efficacy in adults and adolescents using 4mg, 8 mg or 12 mg of perampanel, with significant results in comparison to placebo for the two highest dosages. This non-significant result for the 4 mg dosing however does not allow to draw any firm conclusion regarding the lack of efficacy of this dosage and does not challenge the known efficacy results for perampanel in the studied population, mainly in adults.

For the paediatric subgroup, the results showed that the median treatment differences in seizure frequency from placebo are weak for the perampanel 4 and 8 mg groups (4.09% and -12.68%

respectively) and rather high for the perampanel 12 mg group (-51.62%). The MAH provided a detailed table with the median percent change in seizure frequency per 28 days in paediatrics during the Core study and the extension study for each dosage compared to placebo. These results are discussed by the MAH. In the same manner, the results showed that the responder rate is weaker for the perampanel 4 and 8 mg groups (% and % respectively) than for placebo (%) and rather high for the perampanel 12 mg group %). The MAH provided a detailed table with the responder rate in paediatrics during the Core study and the extension study for each dosage compared to placebo. These results are discussed by the MAH. Overall, as for the median percent change in seizure frequency, the overall same trend for the responder rate is observed for the low and high perampanel doses. The main drawback for interpretation is probably linked to the low number of paediatrics which did not allow to draw any precise and robust conclusion. Therefore, although no specific conclusion could be drawn from this additional analysis, this issue is not pursued and considered solved as it did not put in question the recommended daily dose of perampanel in the studied population as agreed in the PI.

Regarding the safety, the AEs described in Study 335 are overall consistent with the known safety profile for Fycompa described in the SmPC. The safety results of the study reported that 113 subjects (16.6%) experienced at least one SAEs. When scrutinizing more in detail with PT classification, the most common AE from MedDRA SOC Nervous System Disorders are those already stated in the SmPC: dizziness and somnolence. For the MedDRA SOC Psychotic Disorders, the most common AE are irritability, aggression and agitation. Events reported in patients who had medical history of suicidal behaviours were consistent with the known safety profile of perampanel or could also be related to the medical history of the patients. In some cases, the dose decrease was an option to continue the treatment. In other cases, the subjects discontinued the study or study treatment. A total of 7 deaths were reported in the study with only one in a paediatric subject [redacted] whose death is not related to the study drug.

From these data, no further safety conclusion could be drawn regarding the paediatrics for the following reasons: they represent only 11% of the overall included patients and the MAH did not provide separate data for patients aged 12 to 17 years, as the data are mixed for the overall included patients. This issue is a flaw of this study however not pursued.

As detailed recently in the PSUSA for perampanel, available post marketing data since the marketing authorization in July 2012 did not show additional risks associated with long-term use of perampanel. Nevertheless, post-marketing studies are ongoing and long term safety in adolescents and adults should remain a missing information in the PSUR.

Overall, there were no significant changes in the frequency and severity of previously identified adverse reactions. On the basis of the review of the AEs and TEAEs in this study, no additional changes to the safety information of the SmPC are requested by the Applicant which is acceptable.

3. Rapporteur's CHMP overall conclusion and recommendation

The MAH submitted the results of study 335 in order to fulfil the requirement of reporting paediatric data as outlined in accordance with Article 46 of regulation (EC) no 1901/2006, as amended. The fulfilment of this requirement is questionable regarding the small number of paediatrics included in this study (i.e. 11% of the patients).

However, the MAH provided responses to the request for supplementary information as part of this procedure (see section "Additional clarification requested") and the issues raised are not pursued and considered solved.

The MAH determined that the benefit-risk ratio for Fycompa remains unchanged and positive for the three dosages of perampanel despite the non-significant efficacy result at the end of core study for the 4 mg dosage. Indeed, the results of this study are considered as supportive of the known safety profile and efficacy results of perampanel in adults and adolescents above 12 years of age and do not allow to draw any further robust conclusion.

The MAH does not propose any changes of the currently approved SmPC based on the present data, which is supported.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. For the paediatric subgroup, the subanalysis concluded that the median treatment differences in seizure frequency from placebo are weak for the perampanel 4 and 8 mg groups (4.09% and -12.68% respectively) and rather high for the perampanel 12 mg group (-51.62%). The MAH is requested to provide a detailed table with the median percent change in seizure frequency per 28 days in paediatrics during the Core study and the extension study for each dosage compared to placebo. These results should be discussed by the MAH.
2. In the same manner, the subanalysis concluded that the responder rate is weaker for the perampanel 4 and 8 mg groups (13% and 20% respectively) than for placebo (25%) and rather high for the perampanel 12 mg group 78.6%). The MAH is requested to provide a detailed table with the responder rate in paediatrics during the Core study and the extension study for each dosage compared to placebo. These results should be discussed by the MAH.

The timetable is a 30-day response timetable without clock stop.

MAH responses to Request for supplementary information

The MAH provides responses to the RSI.

1. For the paediatric subgroup, the subanalysis concluded that the median treatment differences in seizure frequency from placebo are weak for the perampanel 4 and 8 mg groups (4.09% and -12.68% respectively) and rather high for the perampanel 12 mg group (-51.62%). The MAH is requested to provide a detailed table with the median percent change in seizure frequency per 28 days in paediatrics during the Core study and the extension study for each dosage compared to placebo. These results should be discussed by the MAH.

MAH's response:

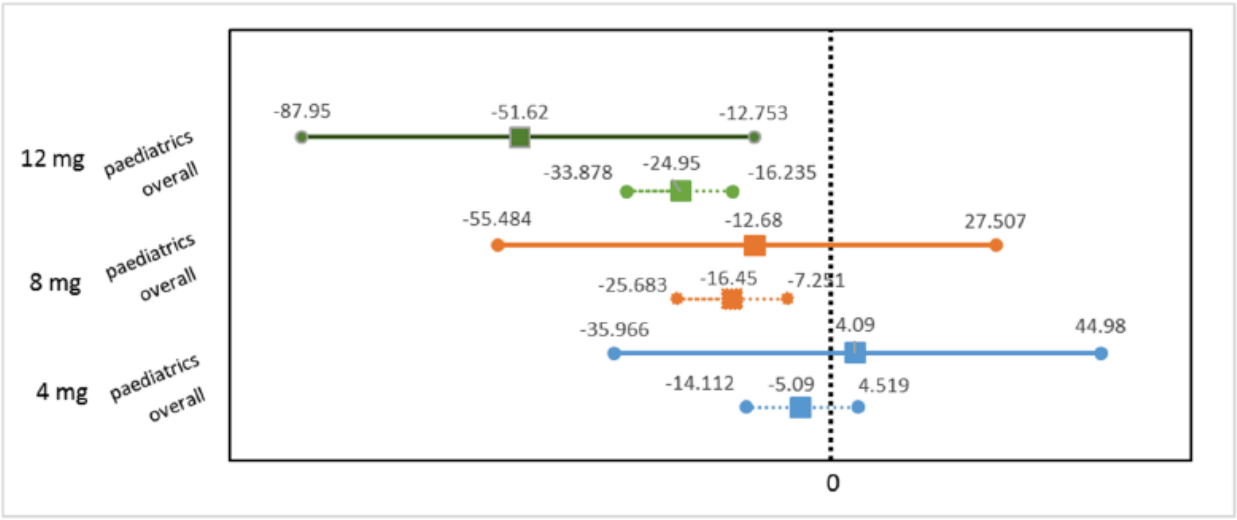
The percent change from baseline in seizure frequency per 28 days, as along with the treatment differences compared to placebo, during the Core study was provided for each dose group by age subgroup in the Core CSR Table 14.2.1.1.1.1.6. For ease of reference, this table is presented in this response as Table 1.

During the Core study, the treatment effect based on the overall study population showed a similar dose-response relationship as for the pediatric subgroup, with increasing median treatment difference from placebo as the dose increased (overall study population: -5.09%, -16.45%, and -24.95% and

pediatric subgroup: 4.09%, -12.68%, and -51.62% for the perampanel 4, 8, and 12 mg groups, respectively). Based on rank ANCOVA, the treatment differences from placebo in the Core Study were statistically significant for the perampanel 8 mg group (P=0.0003) and 12 mg group (P<0.0001), but not for the perampanel 4 mg group (P=0.2330). Therefore, in this study, the weak efficacy for the 4 mg dose group was observed not only in the paediatric subgroup but also in the overall study population (of which majority [87.9%] were adults aged 18 to <65 years).

Shown in Figure 1 is a forest plot depicting the median treatment differences in seizure frequency from placebo for the overall study population and the paediatric subgroup (12-<18 years) by each dose. Note that there was a much larger variability in paediatric data and that the 95% confidence intervals (CI) for the paediatric data overlapped with the corresponding 95% CI for the overall study population for the respective dose group (Table 1). This suggests that there may not be a true difference in the treatment effect or dose-response relationship of perampanel in pediatric (12 to <18 years) vs adult (18 years and older) subjects. Rather it may reflect a large variability due to the small number of subjects in the paediatric subgroup (n=12 to 25 per treatment group) relative to the adult/older subgroup (n=146 to 164 per treatment group).

Figure 1 Forest Plot of Mean Treatment Differences in Change from Baseline Seizure Frequency per 28 Days in Study 335



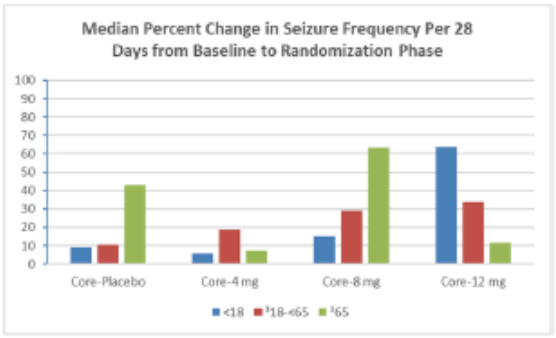
Source: Core CSR Table 14.2.1.1.1.1.1 and Table 14.2.1.1.1.1.6

In the Extension Phase, subjects previously assigned to the placebo group were switched to receive perampanel treatment at starting dose of 2 mg per day and up-titrated to reach individual subject's optimal maintenance dose (not to exceed 12 mg per day). Subjects previously assigned to perampanel 4, 8, or 12 mg groups continued to receive perampanel treatment in Extension Phase. For subjects who achieved 4 or 8 mg/day during the Core study, up-titration of perampanel dose was allowed during Extension Phase to reach individual subject's optimal maintenance dose (not to exceed 12 mg per day).

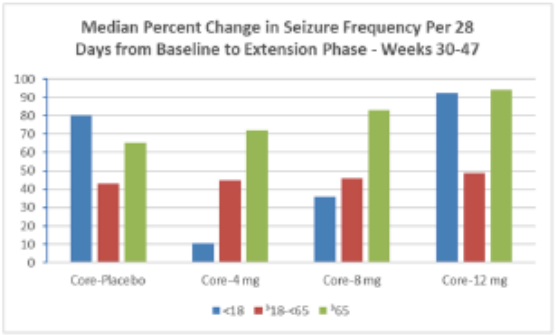
The median percent change from baseline in seizure frequency per 28 days during Extension Phase was provided for each dose group by age subgroup in the Extension CSR Table 14.2.1.2.1.1.1.2 (pages 700 – 701). For ease of reference, the data are presented in this response as Table 2 and Figure 2.

Figure 2 **Median Percent Change from Baseline in Seizure Frequency Per 28 Days During (a) Core Study Randomization Phase and Following Long-Term Open-Label Perampanel Treatment in Study 335**

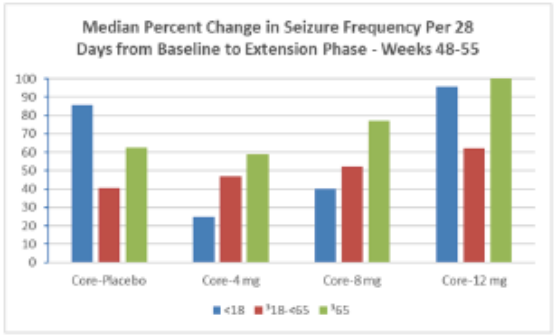
a) Core Study (Randomization Phase)



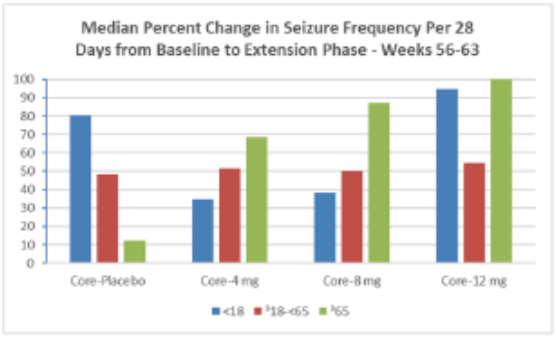
b) Extension Maintenance Phase – Weeks 30-47



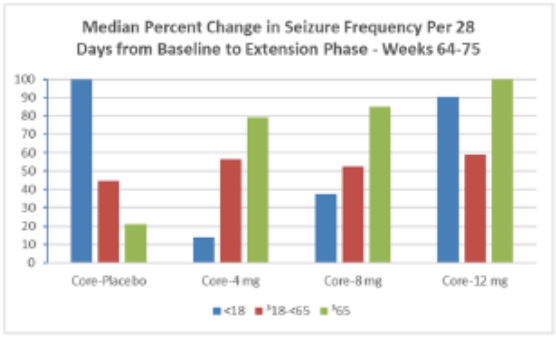
c) Extension Maintenance Phase – Weeks 48-55



d) Extension Maintenance Phase – Weeks 56-63



e) Extension Maintenance Phase – Weeks 64-75



Source: Extension CSR Table 14.2.1.2.1.1.1.2

Note: Treatment group designation is based on the treatment assignment in the Core Study. In the Extension Phase (Figures 2b-2e), all subjects received perampanel treatment including up-titration of perampanel dose to reach individual subject's optimal maintenance dose (not to exceed 12 mg per day).

Overall, the patterns observed in the median percent change in seizure frequency per 28 days across the treatment groups in the Core Study continued into the Extension Maintenance Phase (Figure 2). For example, the median percent change in seizure frequency per 28 days remained relatively low in the pediatric subgroup compared to adult subgroup in the Core-4 mg treatment group.

Eisai examined demographic and baseline characteristics of the pediatric subgroup vs the overall study population by treatment groups in Study 335 (Table 3), with focus on clinical factors that have been identified as potential predictive factors for achieving a major treatment effect in patients with refractory partial-onset seizures with or without secondarily generalized seizures using data from three Phase 3, double-blind, placebo controlled studies (E2007-G000-304 [Study 304], E2007-G000-305 [Study 305], and E2007-G000-306 [Study 306]), as well as their open-label Extension study (E2007-G000-307 [Study 307]) (data on file). These factors are: (a) presence of secondarily generalized tonic-clonic seizures (SGTCS) during baseline, higher perampanel plasma concentration, older age at diagnosis, and lower baseline seizure frequency in the double-blind studies; and, (b) lower baseline seizure frequency, absence of complex partial seizures at baseline, presence of SGTCS during baseline, lower number of baseline AEDs, absence of enzyme-inducing antiepileptic drugs (EIAEDs; defined as carbamazepine, oxcarbazepine, and phenytoin) during baseline, older age at diagnosis, and absence of structural etiologies in the open-label extension study. Examination of the demography and baseline profile data in Study 335 (Table 3) shows similar characteristics between the pediatric subgroup and the overall study population across treatment groups, except for the presence of structural etiologies in 17.4% vs 0% of pediatric subjects in the 4-mg dose group vs placebo group that might partially explain for the "weak" effect seen in the 4-mg pediatric subgroup relative to placebo.

To further investigate why the low dose (4-mg) group in Study 335 did not show statistically significant benefit compared to placebo, Eisai examines the data from Study a previous Phase 3, multicenter, double--blind, randomized, placebo--controlled study (E2007-G000-306; Study 306) that evaluated the efficacy of perampanel (2, 4, and 8 mg/day) given as an adjunctive therapy in adolescent and adult subjects (12 to 72 years of age) with refractory partial seizures. In Study 306, statistically significant benefit was demonstrated for the primary efficacy outcome measure percent change in seizure frequency per 28 days including the 4-mg dose group, compared to placebo.

Table 4 shows the demography and baseline characteristics of subjects in the 4-mg and 8-mg dose groups with focus on clinical factors that may affect efficacy outcome measures in Study 335 and Study 306. Consequently, the proportions of subjects who had 3 or 4 concomitant AEDs and the proportion of subjects who were taking concomitant EIAED at baseline were slightly higher in Study 335 than those in Study 306 8 mg. This suggests a more refractory patient population may have been entered into Study 335 and the concomitant inducer (which lowers perampanel plasma concentrations which in turn) may might be associated with the lower treatment effects of perampanel observed in Study 335, relative to Study 306.

For the completeness of tables with thorough data (table 1 to 5), see the MAH's response document.

CHMP comment:

During the Core study, the treatment effect in the overall study population showed a similar dose-response relationship in the paediatric subgroup, with median treatment difference from placebo increasing with the dose: overall study population: -5.09%, -16.45%, and -24.95% and paediatric subgroup: 4.09%, -12.68%, and -51.62% for the perampanel 4, 8, and 12 mg groups, respectively. These results were statistically significant for the perampanel 8 mg group (P=0.0003) and 12 mg group (P<0.0001), but not for the perampanel 4 mg group (P=0.2330). The MAH concluded that the weak efficacy for the 4 mg dose group was similarly observed in the paediatric and in the overall study population (with nearly 90% of adults aged 18 to <65 years).

It should be highlighted that the dose-response relationship is more "abrupt" in paediatrics (from 4.09% to -51.62%) than in the overall population (from -5.09% to -24.95%) where the relationship is more "progressive". The MAH explains this kind of relation by a larger variability in the paediatrics data with larger confidence intervals in comparison to the CI in the overall population (comprising nearly

90% of adults). This aspect may be due to the small number of paediatrics per treatment groups which enlarges the CI. This is acceptable as regards the low number of patients in each dosing group: 23 patients in the 4 mg group, 25 patients in the 8 mg group and 14 patients in the 12 mg group.

The pattern of change observed in the core study was rather similar in the extension phase with a median percent change in seizure frequency per 28 days in the 4 mg treatment group relatively low in the paediatric subgroup compared to the adult subgroup. The MAH suggested that potential predictive factors like the kind of seizures or their severity could offer some explanation and clarified that the demography and baseline profile data showed similar characteristics between the paediatrics and the overall study population across treatment groups, except for the presence of structural etiologies more frequently observed in paediatrics receiving 4 mg perampanel than in paediatrics receiving placebo (17,4% vs 0%). These aspects could be, according to the MAH, a justification for the "weak" effect seen in the 4mg perampanel group in paediatrics, considering that 17% of 23 patients (= almost 4 patients) are more "severe" in the 4 mg group. This interpretation is uncertain and it should rather be kept in mind that the 4 mg dose is mainly used as an intermediate dose in the titration scheme with a recommended maintenance dose of 8 mg (until 12 mg if necessary).

Regarding Figure 2, the median percent change from baseline in seizure frequency per 28 days during the different maintenance phases for the 12 mg perampanel group is systematically higher in the paediatrics (and in the elderly i.e. > 65 years) than in the overall adult study population which could be linked to a higher exposure to perampanel of paediatrics (and elderly) in comparison to adults, similarly to what was seen, from a PK point of view, within the scope of variation II/47 for the paediatric data.

Finally, for the 8 mg perampanel group, no specific comment is raised regardless of the age group.

Overall, all these results should be considered with caution regarding the low number of paediatrics for each dosing group.

To conclude, the MAH provides further analyses of paediatric data during the core study in comparison to the overall adult and elderly population, for each dosage and discussed them. The dose response relationship in paediatrics is similar to that in adults, with however less precise CI around the median change in seizure frequency which is probably related to the low number of paediatrics in each treatment subgroup. Although no specific conclusion could be drawn from this additional analysis, this issue is not pursued and considered solved as it did not put in question the recommended daily dose of perampanel in the studied population as agreed in the PI.

2. In the same manner, the subanalysis concluded that the responder rate is weaker for the perampanel 4 and 8 mg groups (13% and 20% respectively) than for placebo (25%) and rather high for the perampanel 12 mg group 78.6%). The MAH is requested to provide a detailed table with the responder rate in paediatrics during the Core study and the extension study for each dosage compared to placebo. These results should be discussed by the MAH.

MAH's response:

The requested analysis was provided in the CSR for Study 335 as Table 14.2.1.2.2.1.1.2, pages 766 – 767. For ease of reference this sub-group analysis is presented in this response as Table 5.

As well as percent change in seizure frequency, the trend is similar in responder rate.

This result is also considered to be related to the severity of the patients who entered in this study.

At Core study, the responder rate of 4 and 8 mg paediatric subgroups was low. During the extension phase, the responder rate gradually increased up to 40-50%. However, the responder rate was dramatically increased during the extension phase in patients who took placebo at Core study. Due to the small number of patients, the reason of the different response is unknown.

CHMP comment:

The MAH provides further data regarding the responder rate and discussed them. The additional interpretation for the weaker responder rate for the perampanel 4 and 8 mg groups (13% and 20% respectively) than for placebo (25%) and rather high for the perampanel 12 mg group 78.6% is not convincing. However, as for the median percent change in seizure frequency, the overall same trend for the responder rate is observed for the low and high perampanel doses. The main drawback for interpretation is probably linked to the low number of paediatrics which did not allow to draw any precise and robust conclusion. Therefore, although no specific conclusion could be drawn from this additional analysis, this issue is not pursued and considered solved as it did not put in question the recommended daily dose of perampanel in the studied population as agreed in the PI.